M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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Date: October 12, 2000

To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: ANDAs

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: Blend Uniformity Analysis Draft Guidance

Presented for: PQRI Workshop on Blend Uniformity

Date Presented: September 7, 2000

Presented by: Frank Holcombe, Jr., Ph.D.

Number of Pages: 12

Melissa Lamb

Attachment

90S-0308

M691

PQRI Workshop on

Blend Uniformity

ANDAs: Blend Uniformity Analysis

Draft Guidance

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September 7, 2000

Background:

- In-Process Controls for ANDAs
- Applicant Questions/Complaints to OGD Management
- Internal Discussion/External Evaluation
- Consistent Review Practice Defined
- Guidance (for Industry) Developed
- Draft Guidance for Industry Published (8/99)

Guidance Contents:

- Intended for ANDAs (Original and Certain Supplements)
- Used 21 CFR 211 and 21 CFR 314 (Relating to In-Process Controls)
- Described Extent of Coverage for Dosage Forms, Composition
- Described Sampling and Test Acceptance Criteria

Guidance Contents:

- Coverage Included Application and Production Batches
- Based in Part on USP Content Uniformity Chapter
- Complex Products Addressed on Case by Case Basis
- Was an Application, Not a GMP Requirement

Guidance Contents - Sampling:

- NMT 3X Dosage Unit Weight
- Increase to NMT 10X
  (if Sampling Bias Demonstrated)
- Sampling Locations not Restricted (Blender or Containers)
- Six to Ten Samples, No Composites
- Analysis Sample Equivalent to One Dosage Unit Weight

Guidance Contents - Analysis:

- Individual, Mean, RSD
- Range of Mean - 90% - 100%
- RSD NMT 5.0%
- Multi-Tier Testing Not Recommended

Background:

- Comments Received
- Internal Evaluation/Discussions
- Unexpected Level of Reaction to Guidance
- Ongoing Revision
- Involvement with PQRI
- PQRI Drug Product Technical Committee Priority
- PQRI Workshop

Issues/Concerns:

- Concepts
    - Use Beyond ANDAs
    - Differences Between NDA and ANDA
    - Deletion of Testing Requirement
    - Inappropriate Test for Validated Process
    - Center Review or Field GMP Issue

Issues/Concerns:

- **Technical Areas**
    - **Problems Inherent in Sampling of Solid Heterogeneous Systems**
    - **Sample Sizes**
    - **Analytical Sample Preparation**
    - **Treatment of OOS Results / Multi-Tier Testing Procedures**
    - **Basis for Acceptance Criteria**

Revision:

- **Concepts**
  - **Use Beyond ANDAs - NO**
  - **Differences Between NDA and ANDA - Explanation**
  - **Deletion of Testing Requirement - Provision for Deletion**

Revision:

- **Technical Areas**
  - **Sample Sizes - Relaxation of Recommendation**
  - **Analytical Sample Preparation - Relaxation of Recommended Sample Size**
  - **OOS Results - Potential Basis for Alternate Methods/Criteria for Homogeneity Demonstration**

Remaining Issues/Concerns:

- Problems Inherent in Sampling of Solid Heterogeneous Systems
- Inappropriate Test for Validated Process
- Multi-Tier Testing Procedures
- Basis for Acceptance Criteria